REVIEW

A Systematic Review and Meta-analysis of Randomized Controlled Trials on the Effects of Turmeric and Curcuminoids on Blood Lipids in Adults with Metabolic Diseases

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ABSTRACT

Dyslipidemia is a global health problem and a high risk factor for atherosclerosis, which can lead to serious cardiovascular disease (CVD). Existing studies have shown inconsistent effects of turmeric and curcuminoids on blood lipids in adults. We performed this systematic review and meta-analysis to evaluate the effects of turmeric and curcuminoids on blood triglycerides (TG), total cholesterol (TC), LDL cholesterol, and HDL cholesterol. We searched the English databases of the Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, and the Cochrane Library and 2 Chinese databases, Wanfang Data and China National Knowledge Infrastructure, for randomized controlled trials (RCTs) that studied the effects of turmeric and curcuminoids on blood TG, TC, LDL cholesterol, and HDL cholesterol in subjects with metabolic diseases. With random-effects models, separate meta-analyses were conducted by using inverse-variance. The results are presented as the mean difference with 95% CIs. Evidence from 12 RCTs for TG, 14 RCTs for TC, 13 RCTs for LDL cholesterol, and 16 RCTs for HDL cholesterol showed that turmeric and curcuminoids could lower blood TG by −19.1 mg/dL (95% CI: −31.7, −6.46 mg/dL; $P = 0.003$), TC by −11.4 mg/dL (95% CI: −17.1, −5.74 mg/dL; $P < 0.0001$), and LDL cholesterol by −9.83 mg/dL (95% CI: −15.9, −3.74 mg/dL; $P = 0.002$), and increase HDL cholesterol by 1.9 mg/dL (95% CI: 0.31, 3.49 mg/dL; $P = 0.02$). In conclusion, turmeric and curcuminoids can significantly modulate blood lipids in adults with metabolic diseases. However, these findings should be interpreted cautiously because of the significant heterogeneity between included studies ($I^2 > 50\%$). There is a need for further RCTs in future. *Adv Nutr* 2019;10:791–802.

Keywords: turmeric, curcuminoids, triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol, lipids

Introduction

Metabolic diseases are the result of complex interaction between genes and the environment (1). Metabolic diseases commonly include type 2 diabetes mellitus (T2DM), prediabetes, overweight, obesity, metabolic syndrome (MetS), hyperlipidemia, and nonalcoholic fatty liver disease (NAFLD) (2). It has been widely demonstrated that subjects with metabolic diseases have a higher risk of dyslipidemia. Existing studies have revealed that subjects with T2DM have a higher incidence of dyslipidemia than those with good health (3). In addition, close relationships have been illustrated between dyslipidemia and overweight, obesity, and NAFLD. Some studies have been conducted to clarify that both children and adults with overweight or obesity are more likely to have dyslipidemia and MetS (4, 5). Similarly, patients with NAFLD are susceptible to dyslipidemia, and regulating lipid metabolism is a therapy goal (6, 7). The complicated interactions among these metabolic diseases could have further negative influences on atherosclerosis and coronary heart disease, which can lead to serious heart attack and stroke (8, 9). Hence, dyslipidemia is the main risk factor for cardiovascular disease (CVD), which accounts for approximately half of deaths in Europe (10). Dyslipidemia is characterized by increased triglycerides (TG), total cholesterol (TC), and/or LDL cholesterol and/or decreased HDL cholesterol (11). Although statins are the most popular and effective drugs that are used to lower blood lipids, their inherent disadvantages,

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Abbreviations used: CVD, cardiovascular disease; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

such as increasing the risk of new-onset diabetes and myasthenia, cannot be ignored (12, 13). Some scientists continue to stress the need for novel nonstatin drugs to manage dyslipidemia (14).

Turmeric (*Curcuma longa* L.) is a well-known traditional Chinese medicine, which functions to facilitate blood circulation and to relieve pain. Currently, it is used to treat pain (e.g., postoperative pain, osteoarthritis, etc.) and cancers (e.g., breast cancer, pancreatic cancer, etc.) (15–18). Curcuminoids, the biologically active ingredients of turmeric, consist of curcumin, demethoxycurcumin, and bisdemethoxycurcumin (19). Besides their antipain and anticancer properties, curcuminoids can relieve acute inflammation (e.g., airway inflammation, drug-induced inflammation) and major depression (20–23). In addition, some experiments have demonstrated that curcuminoids function well in reducing hyperglycemia (24, 25). These properties are likely related to the effects of curcuminoids on inflammation in people with T2DM or metabolic syndrome (26). Turmeric and curcuminoids also exhibit lipid-lowering effects, and it is postulated that upregulating adiponectin and reducing resistin and leptin might be responsible for these (27). However, in clinical settings, the effects of turmeric and curcuminoids on lipids are controversial (28–41). Two existing meta-analyses came to different conclusions on the effect of curcuminoids on blood lipids (42, 43). Evidence from 7 trials concluded that curcuminoids had positive effects on blood TG and LDL cholesterol, but little influence on TC and HDL cholesterol in subjects with CVD risk factors (43). Data from 5 trials summarized that curcuminoids did not benefit TG, TC, LDL cholesterol, or HDL cholesterol (42). The reliabilities of those meta-analyses could be seriously impaired by the small number of trials included and the relatively high heterogeneity among studies. Consequently, we performed a meta-analysis on the effects of turmeric and curcuminoids on blood lipid metabolism in adults with metabolic diseases.

Methods

Search strategy

We searched the electronic bibliographic databases of the Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, and the Cochrane Library, and 2 Chinese databases, Wanfang Data and China National Knowledge Infrastructure (CNKI), for RCTs without any limitations of language or time. The representative search strategy in PubMed was as follows: "(curcumin OR curcuminoid OR curcuminoids OR *Curcuma* OR *Curcuma longa* OR turmeric OR *C. longa* OR *Curcuma domestica*) AND (metabolic syndrome OR overweight OR obese OR obesity OR hepatic adipose infiltration OR fatty liver OR hyperuricemia OR hyperinsulinemia OR hyperglycemia OR diabetes mellitus OR glucose OR insulin resistance OR glycemic OR glycaemic OR hypertension OR hyperlipidemia OR lipid metabolism OR dyslipidemia OR hypercholesterolemia OR hypertriglyceridemia OR low-density lipoprotein cholesterol OR LDL-c OR high-density lipoprotein cholesterol OR HDL-c OR total cholesterol OR TC OR triglycerides OR TG OR adipokine OR adiponectin OR adiponectins OR leptin OR leptins) AND (Clinical Trial [ptyp] AND Humans [MeSH] AND Clinical Trial [ptyp] Sort by: Best Match)." In addition, we searched for studies by hand by studying similar articles and obtained the data from authors via email if the primary data were inaccessible.

Study inclusion criteria

After comprehensive reading, studies were selected if they met the following criteria: *1*) the duration of the experiment was not <4 wk; *2*) turmeric and its active ingredients were the only supplement to the same intervention as given to the control group; *3*) the subjects suffered from metabolic diseases (e.g., T2DM, prediabetes, dyslipidemia, overweight, obesity, metabolic syndrome, or NAFLD); *4*) parallel or crossover RCTs were performed in human beings rather than animals; *5*) all data were accessible, including the baseline and endpoint values or net changes between the 2 points with mean, SD, SE, number of participants (*n*), or 95% CIs for the experimental and control groups; *6*) all trials reported ≥1 of the following parameters: TG, TC, LDL cholesterol, or HDL cholesterol; *7*) the trials compared the treatment group with a control group; *8*) the experimental and control groups must have been conducted at the same time; *9*) the subjects in both the intervention and control groups were adults; and *10*) the differences in baseline lipid values were not significant in either experimental or control groups.

Data collection and quality assessment

The information collected was: *1*) study characteristics including first author, publication year, study design, oral agent form, dose, and periods of intervention; *2*) participant information including location (continent), physical condition, type of lifestyle, average age, and baseline values of TG, TC, LDL cholesterol, and HDL cholesterol shown as the mean ± SD; and *3*) the baseline and endpoint values or net changes of TG, TC, LDL cholesterol, and HDL cholesterol in treatment and control groups. Based on the *Cochrane Handbook for Systematic Reviews*, if a trial involved different doses, intervention periods or oral agents, we divided them into separate trials with the same control group (44). If the trial included different treatment groups, we only extracted the information about the turmeric or curcuminoids and control groups. If the trial followed a crossover design, we only made use of the data from the first stage before the subjects went into the washout period (45).

According to the *Cochrane Handbook for Systematic Reviews*, assessments of the quality of the selected studies involved 7 aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (46).

Data synthesis and statistics

We collected the mean, SD, and n information from the intervention and control groups. The means and SDs were calculated based on different conversion formulas if the trial did not include them directly (47). For normally distributed studies, the formulas were as follows: mean $_{change}$ = mean $_{posttreatment}$ − mean $_{baseline}$; SD $_{change}$ = SE × square root n or SD $_{change}$ = square root $((SD_{pretreatment})^2 + (SD_{baseline})^2 - 2R \times SD_{pretreatment} \times SD_{baseline})$, assuming a correlation coefficient (R) = 0.5 (48). If 95% CIs were available, SDs were calculated by the following formula: SD = square root n × (upper limit−lower limit)/3.92 or 4.128 when samples included >100 subjects or <60 subjects in the intervention and control groups, respectively. If the data were divided into different subgroups in the treatment and control groups, we merged them with formulas: $n_{merge} = n_1 + n_2$; mean $_{merge} = (mean_1 \times n_1 + mean_2 \times n_2)/(n_1 + n_2)$; SD $_{merge}$ = square root$((n_1 - 1) \times (SD_1)^2 + (n_2 - 1) \times (SD_2)^2 + ((n_1 \times n_2)/n_1 \times n_2) \times (mean_1{}^2 + mean_2{}^2 - 2 \times mean_1 \times mean_2))$. For non-normally distributed data, we considered the median as the mean and obtained the SD with the formula SD = range interquartile/1.35 if there were >100 participants in each group. If studies included <100 participants, the data were not adopted to decrease bias. Then, the comparison of changes between treatment and control groups was performed.

After collecting the data, the meta-analysis was performed by RevMan 5.3 software. With random-effects models, the results were expressed as the mean difference and 95% CI by an inverse-variance. The heterogeneity was inspected by I^2 values and was deemed low, moderate, or high if it was <25%, between 25% and 75%, or >75%, respectively (49). Subgroup analysis and meta-regressions were conducted to determine the source of heterogeneity if the I^2 value was >25%. Funnel plots and Egger's test were used to estimate the publication bias with Stata version 12 software (StataCorp LP). $P < 0.05$ was considered significant.

Results

Characteristics of the included studies

We searched 790 articles in total and sorted them by file manager. A total of 295 duplicates was excluded, and a further 400 studies were removed for different reasons (reviews or meta-analyses, 75; animal or cell experiments, 204; and no relationship, 121). This left 95 papers for further assessment after reading titles and abstracts. After reading the full articles, 81 studies did not satisfy the selection criteria (nonmetabolic disease, 35; mixed interventions, 34; treatment period <4 wk, 4; no control group, 3; unpublished articles, 2; neither English nor Chinese articles, 1; and conference or supplementary papers, 3). A total of 14 studies, including 16 arms, was selected to conduct a comprehensive evaluation (**Figure 1**). Except for 1 trial in Oceania, all of the included studies were conducted in Asia (32). Thirteen arms were double-blind RCTs, of which 1 was crossover and the others were parallel. Another 3 trials were open-label RCTs (34, 35, 37). For the physical condition, 3 studies, including 4 trials, recruited subjects with MetS (28, 29, 33). People with obesity and dyslipidemia were included to study the effects of curcuminoid-piperine on lipids (31). One study evaluated the function of curcumin in people with hypercholesterolemia (32). Two arms had people with NAFLD participate in the experiments (33, 34). Another 8 trials selected subjects with T2DM to complete the studies (35–41). The age of the subjects ranged from 18 to 70 y, and the dose of curcuminoids ranged from 66.3 mg/d to 1795 mg/d. The sustained intervention periods ranged from 4 wk to 6 mo. All trials made use of uniform-appearing capsules, except 1 trial that used tablets (32). The oral agents varied from traditional agents (e.g., turmeric, curcumin, and curcuminoids) to innovative agents (e.g., curcuminoid-piperine, nanocurcumin). Regarding the basic concentrations of lipids, the baseline values of TG in 2 trials in the experimental group were significantly higher than those in the control group (33, 34); 1 study stated that the baseline values of TC and LDL cholesterol in the experimental group were higher than those in the control group (34), whereas 1 study identified the converse situation (41). There was no difference in baseline HDL cholesterol. Two trials, which presented data as medians, proved that the distribution of baseline TG was non-normal (32, 39). In addition, 1 study showed baseline values of TC and LDL cholesterol as medians (30). Some studies included subjects without any other therapy for decreasing lipids (29–35, 37, 40), whereas others recruited people using other essential remedies (28, 36, 38, 39, 41) (**Table 1**). Finally, there were 12 trials for TG (28–31, 35–38, 40, 41), 14 trials for TC (28, 29, 31–33, 35–41), 13 trials for LDL cholesterol (28, 29, 31–33, 35–40), and 16 trials for HDL cholesterol (28–41).

Assessment of quality and publication bias

More than half of the trials did not clearly state the generation of random sequences (30–37, 41). Regarding the concealment of allocation, 4 trials did not present the details of the concealment procedure (31–33, 41), and 3 trials had a high risk of concealment bias (34, 35, 37). The outcome assessment blinding was unclear in 2 trials (31, 33). In addition, 2 studies were unclear about other biases (31, 32) (**Table 2**).

Egger's test proved that there was no publication bias in TG, TC, LDL cholesterol, or HDL cholesterol, with P values equal to 0.178, 0.707, 0.052, and 0.92, respectively. Funnel plots also showed that the distribution of trials was symmetric (the figures are not shown).

Effect on TG

Twelve trials with 592 and 591 participants in the intervention and control groups, respectively, included circulating TG concentration data. With random-effects models, the difference in average net changes in TG concentrations between the treatment and control groups was −19.1 mg/dL (95% CI: −31.7, −6.46 mg/dL). The I^2 value was 75%, and

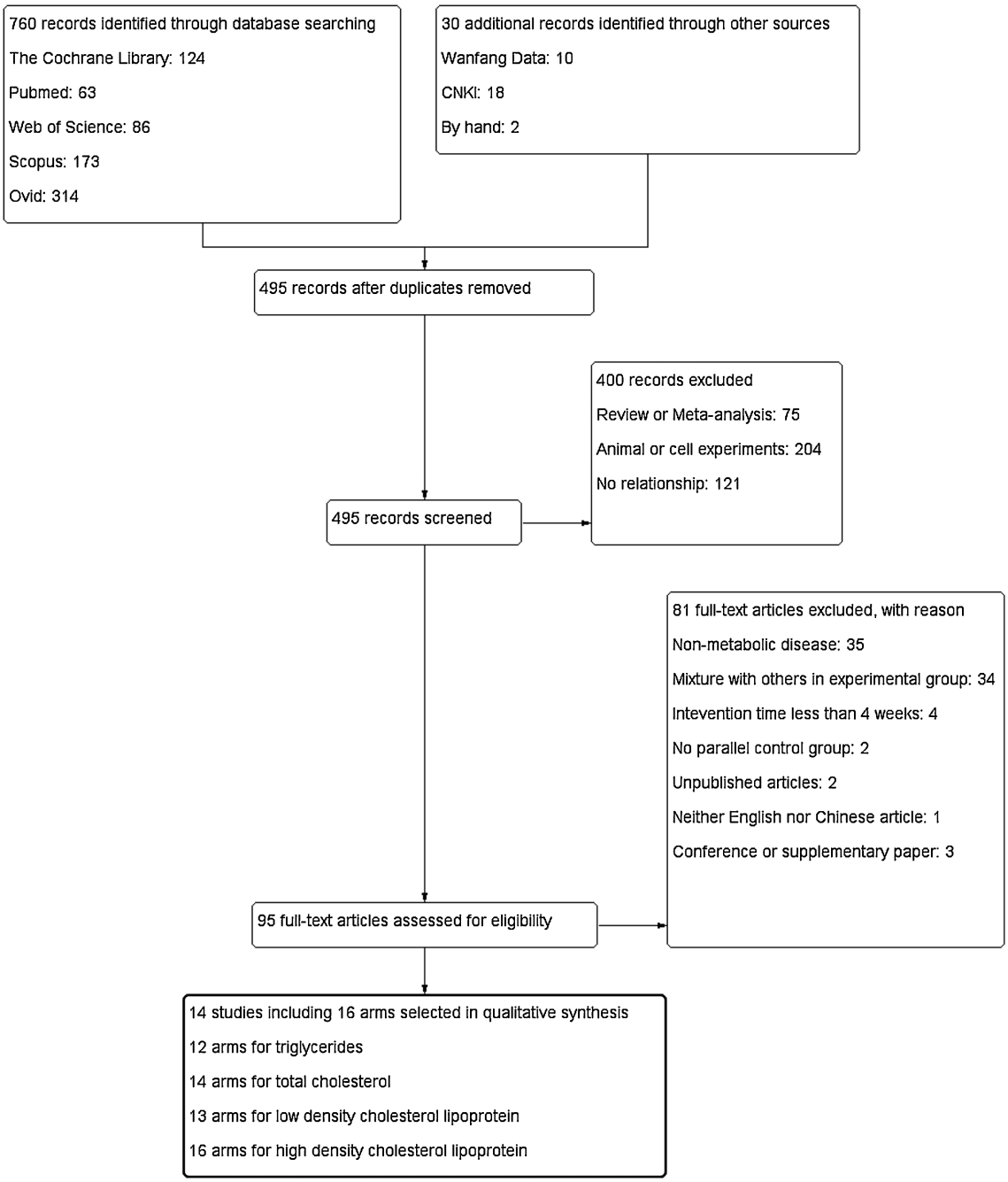

FIGURE 1 Database search and study selection. We searched the English databases of the Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, and the Cochrane Library, and 2 Chinese databases, Wanfang Data and CNKI, for RCTs that studied the effects of turmeric and curcuminoids on blood triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol in subjects with metabolic diseases. By reading titles, abstracts and full articles, we finally selected 16 arms.

the related P value was 0.003. The corresponding results are presented in **Figure 2**. These data showed that turmeric and curcuminoids significantly decreased the concentration of TG.

Effect on TC

Fourteen trials with 632 and 634 participants in the intervention and control groups respectively, included circulating TC concentration data. With random-effects models, the difference in average net change in TC concentrations between the treatment and control groups was −11.4 mg/dL (95% CI: −17.1, −5.74 mg/dL). The I^2 value was 48%, and the related P value was <0.0001. The corresponding results are presented in **Figure 3**. These data showed that turmeric and curcuminoids significantly decreased the TC.

TABLE 1 Characteristics of trials including basic information and baseline lipid concentrations in this meta-analysis[1]

First author, year, ref.	Cont	Study design	Subjects	*N*	Age, y	Baseline TG, mg/dL	Baseline TC, mg/dL	Baseline LDL, cholesterol, mg/dL	Baseline HDL cholesterol, mg/dL	Inter	Dose of Cur (mg/d) and form	Period	Other lipid-lowering therapy	Lifestyle
Ueng, 2014 (28)	Asia	RDP	MetS	T:30 C:29	T:59 ± 10.1 C:59.6 ± 14.1	T: 177 ± 83.7 C:153.4 ± 80.4	T: 196 ± 41.8 C:179 ± 33.3	T:120 ± 36.2 C:107 ± 24.1	T:40.7 ± 8.57 C:41.8 ± 11.8	Cur	1795; cap	12 wk	Yes	NR
Gilani, 2015a (29)	Asia	RDP	Males with MetS	T:63 C:63	T:42.4 ± 13.7 C:41.6 ± 12.8	T:165 ± 40.1 C:164 ± 42.7	T:177 ± 29.6 C:181 ± 23.3	T:111 ± 22.2 C:120 ± 27.3	T:33.9 ± 8.2 C:33.7 ± 7.4	Tur	120; cap	4 wk	No	Modi
Gilani, 2015b (29)	Asia	RDP	Males with MetS	T:63 C:63	T:42.4 ± 13.7 C:41.6 ± 12.8	T:165 ± 40.1 C:164 ± 42.7	T:177 ± 29.6 C:181 ± 23.3	T:111 ± 22.2 C:120 ± 27.3	T:33.9 ± 8.2 C:33.7 ± 7.4	Tur	120; cap	8 wk	No	Modi
Panahi, 2014 (30)	Asia	RDP	MetS	T:50 C:50	T:44.8 ± 8.67 C:43.5 ± 9.7	T:200 C:186[2]	T:220 C:184[3]	T:190 C:157[3]	T:31.5 C:35.5[2]	Cur-p	1000; cap	8 wk	No	Modi
Ferns, 2013 (31)	Asia	RDC	Obese with dyslipidemia	T:15 C:15	18–65[4]	T:106 ± 30.2 C:126.2 ± 57.1	T:196 ± 30.4 C:191 ± 27.7	T:120 ± 23.6 C:120 ± 27.9	T:46.3 ± 9.8 C:46.6 ± 7.8	Curn	1000; cap	30 d	No	Ori
Garg, 2017 (32)	Oceania	RDP	Hypercho	T:18 C:18	18–70[4]	T:109 C:113[3]	T:260 ± 13.9 C:256 ± 6.94	T:171 ± 50.9 C:176 ± 29.6	T:61.5 ± 3.87 C:57.7 ± 4.26	Cur	200; tab	4 wk	No	Modi
Rahmani, 2016 (33)	Asia	RDP	NAFLD with MetS	T:37 C:40	T:46.4 ± 11.6 C:49 ± 9.78	T:200 ± 91.5 C:160 ± 61.9[5]	T:199 ± 41.8 C:187 ± 33	T:107 ± 31.4 C:116 ± 22.3	T:44.3 ± 11.8 C:42.6 ± 6.67	Cur-f	70; cap	8 wk	No	NR
Panahi, 2016 (34)	Asia	RP	NAFLD	T:44 C:43	T:45 ± 12.6 C:47.2 ± 10.3	T:151 ± 75.6 C:150 ± 68.5[5]	T:200 ± 40.8 C:184 ± 46.9[5]	T:131 ± 33.5 C:109 ± 46.2[5]	T:46.8 ± 9.84 C:47.4 ± 10.6	Curcur	330; cap	8 wk	No	Modi
Usharani, 2008 (35)	Asia	RP	T2DM	T:23 C:21	T:55.5 ± 10.8 C:49.8 ± 8.18	T:176 ± 27.6 C:170 ± 47.5	T:195 ± 41.2 C:197 ± 35.7	T:120 ± 42.1 C:125 ± 34.9	T:38.8 ± 7.69 C:36.4 ± 7.67	Cur	600; cap	8 wk	No	NR
Khajehdehi, 2011 (36)	Asia	RDP	T2DM	T:20 C:20	T:52.9 ± 9.2 C:52.6 ± 9.7	T:236 ± 147 C:220 ± 107	T:214 ± 66.5 C:193 ± 45.7	T:114 ± 34.6 C:108 ± 39.9	T:43.8 ± 12.6 C:39.8 ± 9.5	Tur	66.3; cap	2 mo	Yes	NR
Maithili, 2014 (37)	Asia	RP	Male T2DM	T:30 C:30	T:47 ± 7.17 C:46.8 ± 6.1	T:121 ± 37.1 C:127 ± 33.3	T:185 ± 14.6 C:182 ± 22.3	T:124 ± 17 C:122 ± 26.3	T:36 ± 8.1 C:34.3 ± 7.1	Tur	46; cap	4 wk	No	NR
Na, 2013 (38)	Asia	RDP	Ow/ob with T2DM	T:50 C:50	T:55.4 ± 6.4 C:54.7 ± 8.34	T:19 ± 47 C:194 ± 92.1	T:236 ± 43.7 C:235 ± 48	T:166 ± 46.4 C:167 ± 44.5	T:53 ± 10.1 C:51.5 ± 10.8	Curn	300; cap	3 mo	Yes	Ori
Kazemi, 2016 (39)	Asia	RDP	T2DM	T:35 C:35	T:563 ± 11.2 C:61 ± 10.8	T:109 C:142[3]	T:163 ± 33.9 C:162 ± 38.6	T:96.6 ± 33.9 C:100 ± 30.3	T:54.3 ± 14 C:60.4 ± 16	Nanocur	80; cap	3 mo	Yes	Modi
Jirawatnotai, 2014a (40)	Asia	RDP	T2DM	T:107 C:106	T:59.2 ± 11 C:60 ± 10.7	T:158 ± 102 C:167 ± 101	T:199 ± 45.1 C:196 ± 44.2	T:118 ± 35.1 C:113 ± 33.3	T:498 ± 10.8 C:49.2 ± 13.1	Curn	1500; cap	3 mo	No	Modi
Jirawatnotai, 2014b (40)	Asia	RDP	T2DM	T:107 C:106	T:59.2 ± 11 C:60 ± 10.7	T:158 ± 102 C:167 ± 101	T:199 ± 45.1 C:196 ± 44.2	T:118 ± 35.1 C:113 ± 33.3	T:49.8 ± 10.8 C:49.2 ± 13.1	Curn	1500; cap	6 mo	No	Modi
Panahi, 2017 (41)	Asia	RDP	T2DM	T:50 C:50	T:43 ± 8 C:41 ± 7	T:230 ± 81.8 C:207 ± 54.6	T:217 ± 41.6 C:231 ± 71	T:169 ± 30.8 C:199 ± 54.52	T:409 ± 5.41 C:39.5 ± 6.09	Cur-p	1000; cap	12 wk	Yes	Modi

[1] Values are means ± SDs unless otherwise indicated. C, control group; Cap, capsule; Cont, continent; Cur, curcumin; Cur-f, curcumin formulation; Curn, curcuminoids; Cur-p, curcuminoids-piperine; Hypercho, hypercholesterolemia; Inter, intervention; MetS, metabolic syndrome; Modi, modifications; N, number of subjects; NAFLD, nonalcoholic fatty liver disease; Nanocur, nano-curcuminoids; NR, not reported; Ori, original; RDC, randomized double-blind crossover; RDP, randomized double-blind parallel; ref, reference; RP, randomized parallel; tab, tablet; T, treatment group; Tur, turmeric; T2DM, type 2 diabetes mellitus.

[2] The data show the means for normal distribution.

[3] The data show the medians for non-normal distribution.

[4] The data are shown as the range.

[5] Significant differences between the experimental and control groups.

TABLE 2 Risk of bias of the random sequence generation, allocation concealment, participant personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias for trials in the meta-analysis based on the Cochrane Risk of Bias Tool[1]

First author, year (ref)	Random sequence generation	Allocation concealment	Participant personnel blinding	Outcome assessment blinding	Incomplete outcome data	Selective reporting	Other bias
Ueng, 2014 (28)	Low	Low	Low	Low	Low	Low	Low
Gilani, 2015a (29)	Low	Low	Low	Low	Low	Low	Low
Gilani, 2015b (29)	Low	Low	Low	Low	Low	Low	Low
Panahi, 2014 (30)	Unclear	Low	Low	Low	Low	Low	Low
Ferns, 2013 (31)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Garg, 2017 (32)	Unclear	Unclear	Low	Low	Low	Low	Unclear
Rahmani, 2016 (33)	Unclear	Unclear	Low	Unclear	Low	Low	Low
Panahi, 2016 (34)	Unclear	High	Low	Low	Low	Low	Low
Usharani, 2008 (35)	Unclear	High	Low	Low	Low	Low	Low
Khajehdehi, 2011 (36)	Unclear	Low	Low	Low	Low	Low	Low
Maithili, 2014 (37)	Unclear	High	Low	Low	Low	Low	Low
Na, 2013 (38)	Low	Low	Low	Low	Low	Low	Low
Kazemi, 2016 (39)	Low	Low	Low	Low	Low	Low	Low
Jirawatnotai, 2014a (40)	Low	Low	Low	Low	Low	Low	Low
Jirawatnotai, 2014b (40)	Low	Low	Low	Low	Low	Low	Low
Panahi, 2017 (41)	Unclear	Unclear	Low	Low	Low	Low	Low

[1]The details were related to 7 domains that contained random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each category contained low risk, high risk, and unclear risk according to their influence on the corresponding studies.

Effect on LDL cholesterol

Thirteen trials with 582 and 584 participants in the intervention and control groups, respectively, included circulating LDL cholesterol concentration data. With random-effects models, the difference in the average net change in LDL cholesterol values between the treatment and control groups was −9.83 mg/dL (95% CI: −15.9, −3.74 mg/dL). The I^2 value was 71%, and the related P value was 0.002. The corresponding results are presented in **Figure 4**. These data showed that turmeric and curcuminoids significantly decreased the concentration of LDL cholesterol.

Effect on HDL cholesterol

Sixteen trials with 726 and 727 participants in the intervention and control groups, respectively, included circulating HDL cholesterol concentration data. With random-effects models, the difference in the average net change in HDL cholesterol concentrations between the treatment and control groups was 1.9 mg/dL (95% CI: 0.31, 3.49 mg/dL). The I^2 value was 70%, and the related P value was 0.02. The corresponding results are presented in **Figure 5**. These data showed that turmeric and curcuminoids significantly increased the concentration of HDL cholesterol.

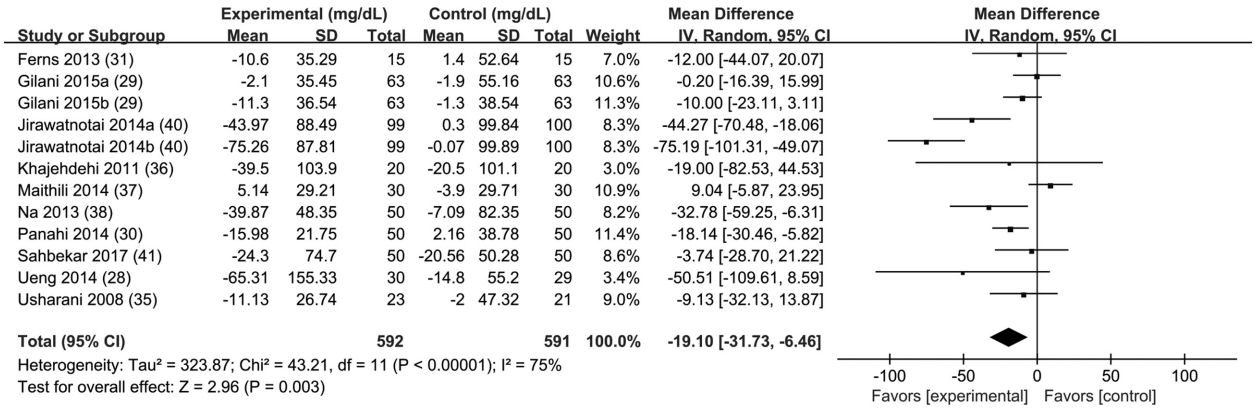

FIGURE 2 Forest plot of the differences in changes in circulating triglycerides in adults with metabolic disease that did or did not receive turmeric or curcuminoids in 12 trials ($n = 1183$). With random-effect models, data were calculated through use of inverse-variance (IV) and presented as the mean difference (black squares), 95% CI (horizontal lines through gray squares), and pooled-effect sizes (black diamonds) with the unit of mg/dL.

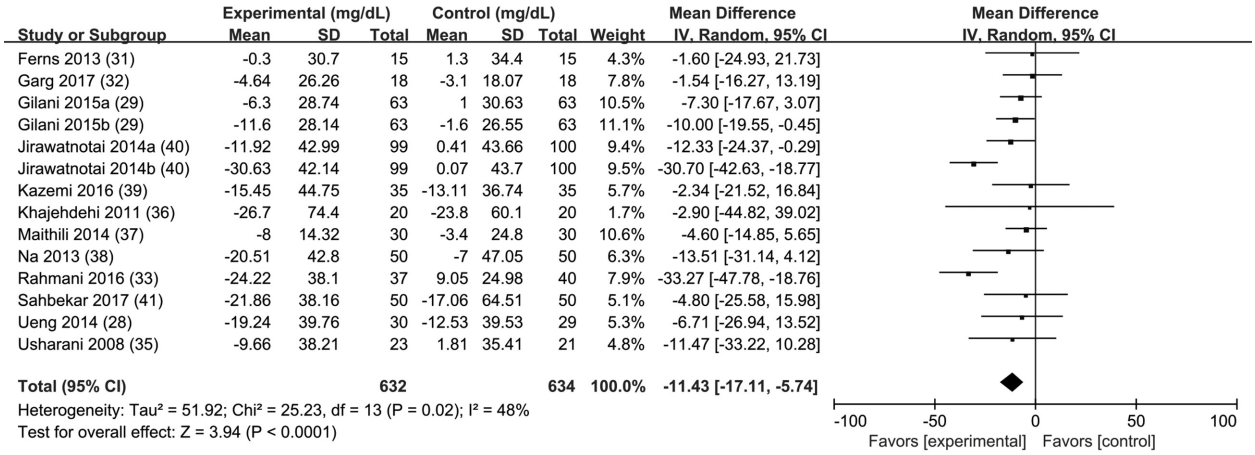

FIGURE 3 Forest plot of the differences in changes in circulating total cholesterol in adults with metabolic disease that did or did not receive turmeric or curcuminoids in 14 trials ($n = 1266$). With random-effect models, data were calculated through use of inverse-variance (IV) and presented as the mean difference (black squares), 95% CI (horizontal lines through gray squares), and pooled-effect sizes (black diamonds) with the unit of mg/dL.

Meta-regressions and subgroup analysis

Meta-regressions were conducted for TG, TC, LDL cholesterol, and HDL cholesterol. We completed meta-regressions from 6 aspects (intervention period and dose, baseline values of lipids, use of other lipid-lowering therapies, administration form, and morbid state of subjects) for each parameter. The results showed that the intervention period [(regression coefficient: −3.89; $P = 0.000$; 95% CI: −5.36, −2.42); (regression coefficient: 0.48; $P = 0.001$; 95% CI: 0.23, 0.74)] and daily dosage of curcuminoids [(regression coefficient: −0.03; $P = 0.007$; 95% CI: −0.049, −0.01); (regression coefficient: 0.004; $P = 0.001$; 95% CI: 0.002, 0.006)] were the main sources of heterogeneity for TG and HDL cholesterol. In addition, the morbid state of subjects was the main source of heterogeneity for TC (regression coefficient: −31.7; $P = 0.045$; 95% CI: −62.5, −0.96). We conducted 3 subgroup analyses depending on the morbid state of the subjects, dose of curcuminoids, and intervention period. The results are shown in **Table 3**.

Discussion

This meta-analysis showed that turmeric and curcuminoids could significantly decrease TG, TC, and LDL cholesterol, and increase HDL cholesterol. Moreover, the stabilities of the conclusions were estimated by removing trials 1 by 1 on RevMan 5.3 software. The stabilities for all blood lipid parameters were outstanding. To be specific, none of the

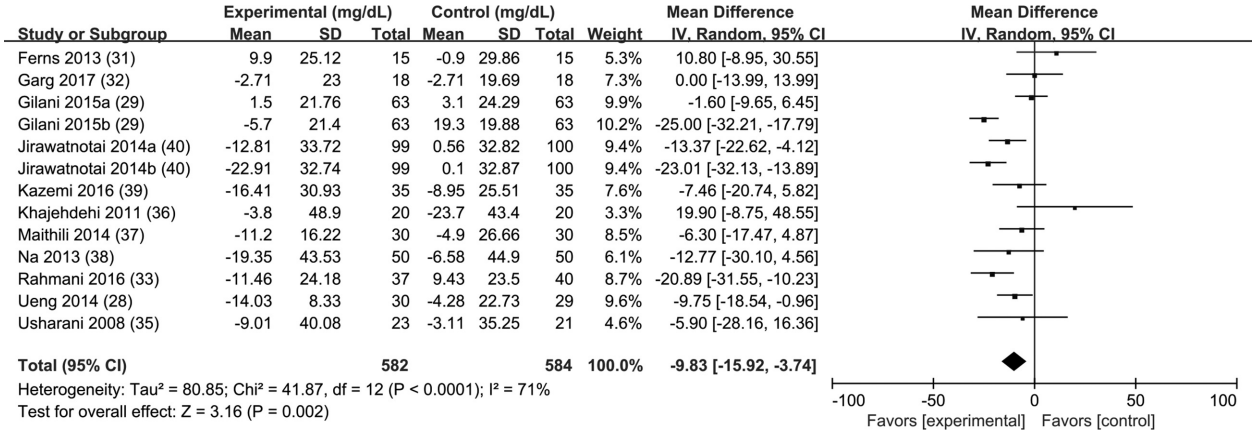

FIGURE 4 Forest plot of the differences in changes in circulating LDL cholesterol in adults with metabolic disease that did or did not receive turmeric or curcuminoids in 13 trials ($n = 1166$). With random-effect models, data were calculated through use of inverse-variance (IV) and presented as the mean difference (black squares), 95% CI (horizontal lines through gray squares), and pooled-effect sizes (black diamonds) with the unit of mg/dL.

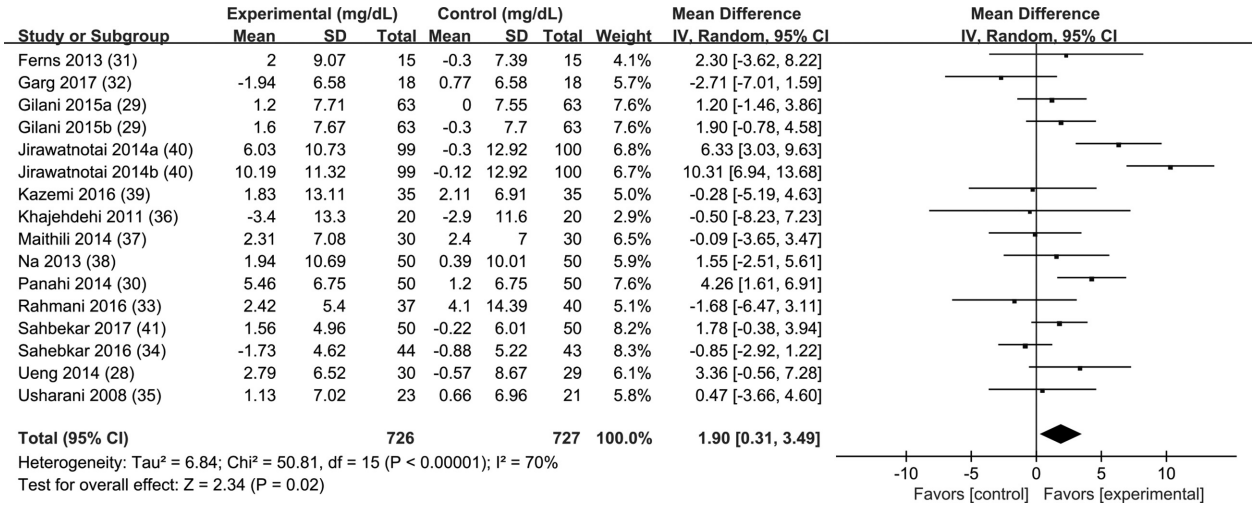

FIGURE 5 Forest plot of the differences in changes in circulating HDL cholesterol in adults with metabolic disease that did or did not receive turmeric or curcuminoids in 16 trials ($n = 1453$). With random-effect models, data were calculated through use of inverse-variance (IV) and presented as the mean difference (black squares), 95% CI (horizontal lines through gray squares), and pooled-effect sizes (black diamonds) with the unit of mg/dL.

results changed by eliminating any 1 arm. The mechanisms of turmeric and curcuminoids that regulate lipid metabolism have been explored in some studies. One study demonstrated that curcumin decreased lipids by inhibiting sterol regulatory element-binding proteins (50). Another study showed that the function of curcumin that improved lipid metabolism was related to repression of the 11β-hydroxysteroid dehydrogenase (51). In addition, curcumin could improve metabolism through different metabolic pathways, such as the TCA cycle, glycolysis, gluconeogenesis, synthesis of ketone bodies and cholesterol, ketogenesis of branched chain amino acids, choline metabolism, and fatty acid metabolism (52).

It was proven that intervention dose and period are the main sources of heterogeneity for TG and HDL cholesterol, while morbid state was closely related to the source of heterogeneity for TC by meta-regressions in our study ($P < 0.05$). Consequently, we conducted 3 subgroup analyses to determine the sources of heterogeneity. There were 4 subgroups of intervention periods (4 wk, 8 wk, 12 wk, and 24 wk subgroups). Turmeric and curcumin had no effect on any lipid in the 4 wk subgroup, and demonstrated no effect on HDL cholesterol in the 8 wk subgroup. These results implied that the efficacy of turmeric and curcumin would be strengthened by increasing the treatment period to $\geq$8 wk. In addition, the heterogeneities for TG in all time-subgroups decreased significantly, even to 0%, in the 4 wk and 8 wk subgroups. Furthermore, when we eliminated 1 study from the 12 wk subgroup (41), the I^2 value decreased from 48% to 0%, but the pooled outcome in this subgroup was not altered. These findings might explain that the different baseline TG concentrations were 1 of the sources of heterogeneity (41). The heterogeneity for HDL cholesterol mainly came from the 8 wk and 12 wk subgroups, with the I^2 values of 53% and 44%, respectively. After removing 1 study from the 8 wk subgroup (30) and another study from the 12 wk subgroup (40), the heterogeneities decreased from 53% and 44% to 0% in the 8 wk and 12 wk subgroups, respectively. These results might be attributed to the highest doses in the 2 trials in both subgroups. In the subgroup of dose of curcumin, the heterogeneities for TG in both the high-dose and low-dose groups were still significant. However, the heterogeneity of the high-dose subgroup abated from 77% to 36% after removing 1 trial without changing the overall effect (40), and the heterogeneity of the low-dose subgroup decreased from 43% to 8% after omitting 1 study (37), while the pooled effect showed no significant difference. The heterogeneities for HDL cholesterol were 82% in the high-dose subgroup and 0% in the low-dose subgroup. The I^2 value for the high-dose subgroup decreased to 33% when 2 trials were eliminated (34, 40). These results might confirm that the intervention time and dose of curcumin were the main sources of heterogeneity for TG and HDL cholesterol between the treatment and control groups. When we removed 2 studies (33, 40), the heterogeneity values for TC dropped markedly from 39% and 43% to 0% in the high-dose and low-dose subgroups, respectively. As a result, the overall heterogeneity of TC decreased from 48% to 0%, and the pooled result did not change. For the subgroup analysis of physiological status, the number of trials that involved people with prediabetes, overweight, obesity, MetS, hyperlipidemia, and NAFLD was too small to conduct subgroup-analysis. Consequently, we only formed the subgroups of subjects with T2DM or non-T2DM (e.g., prediabetes, overweight, obesity, MetS, hyperlipidemia, and NAFLD). The heterogeneities were 84%, 46%, 51%, and 77% in the T2DM subgroup and 15%, 58%, 83%, and 53% in the non-T2DM subgroup for TG, TC, LDL cholesterol, and HDL cholesterol, respectively.

TABLE 3 Subgroup analysis about treatment period, treatment dose, and morbid state of subjects for triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol according to meta-regression analysis[1]

Subgroup	Trials, *n*	Number of subjects (T/C)	Mean difference, 95% CI (mg/dL)	Heterogeneity, I^2	*P*
TG					
Treatment period					
4 wk	3	108/108	3.04 (−7.34, 13.4)	0%	0.57
8 wk	4	156/154	− 13.7 (−22, −5.43)	0%	0.001
12 wk	4	229/229	− 29.1 (−50.3, −7.87)	48%	0.007
24 wk	1	99/100	− 75.2 (−101, −49.2)	Not available	<0.00001
Treatment dose					
High dose (1000–1795 mg/d)	6	343/344	− 32.1 (−53.9, −10.3)	77%	0.004
Low dose (46–600 mg/d)	6	249/247	− 6.3 (−17.2, 4.57)	43%	0.26
Morbid state of subjects					
Subjects with T2DM	7	371/371	− 24.6 (−48.6, −0.59)	84%	0.04
Subjects with non-T2DM	5	221/220	− 11.6 (−20.2, −2.96)	15%	0.008
Total cholesterol					
Treatment period					
4 wk	4	126/126	− 4.82 (−11.1, 1.47)	0	0.13
8 wk	4	143/144	− 16.9 (−31, −2.76)	60%	0.02
12 wk	5	264/264	− 9.23 (−16.8, −1.69)	0	0.02
24 wk	1	99/100	− 30.7 (−42.6, −18.8)	Not available	<0.00001
Treatment dose					
High dose (330–1795 mg/d)	7	366/365	− 13.8 (−22.1, −5.48)	39%	0.001
Low dose (46–300 mg/d)	7	266/269	− 9.58 (−17.3, −1.84)	54%	0.02
Morbid state of subjects					
Subjects with T2DM	8	406/406	− 12 (−20, −4.04)	46%	0.003
Subjects with non-T2DM	6	226/228	− 10.7 (−19.7, −1.73)	58%	0.02
LDL cholesterol					
Treatment period					
4 wk	4	126/126	− 1.53 (−7.20, 4.14)	0	0.6
8 wk	4	143/144	− 13.7 (−27.2, −0.23)	72%	0.05
12 wk	4	214/214	− 10.9 (−16.4, −5.47)	0	<0.0001
24 wk	1	99/100	− 23 (−32.1, −13.9)	Not available	<0.00001
Treatment dose					
High dose (300–1795 mg/d)	6	316/315	− 11.5 (−19.2, −3.73)	55%	0.004
Low dose (46–200 mg/d)	7	266/269	− 8.45 (−18.1, 1.2)	80%	0.09
Morbid state of subjects					
Subjects with T2DM	7	356/356	− 10.7 (−18.1, −3.38)	51%	0.04
Subjects with non-T2DM	6	226/228	− 9.16 (−19.4, 1.04)	83%	0.08
HDL cholesterol					
Treatment period					
4 wk	4	126/126	0.27 (−1.55, 2.09)	0	0.77
8 wk	6	237/237	0.95 (−1.08, 2.99)	53%	0.36
12 wk	5	264/264	2.73 (0.64, 4.82)	44%	0.01
24 wk	1	99/100	10.3 (6.94, 13.7)	Not available	<0.00001
Treatment dose					
High dose (330–1795 mg/d)	8	410/408	3.48 (0.89, 6.06)	82%	0.008
Low dose (46–300 mg/d)	8	316/319	0.49 (−0.83, 1.81)	0	0.47
Morbid state of subjects					
Subjects with T2DM	8	406/406	2.74 (−0.02, 5.5)	77%	0.05
Subjects with non-T2DM	8	320/321	1.09 (−0.60, 2.79)	53%	0.21

[1]The subgroup analysis was performed in 3 fields to discover the sources of heterogeneity for all parameters. The results are shown as the mean difference (mg/dL), 95% CIs and corresponding I^2 values. C, control group; T, treatment group; T2DM, type 2 diabetes mellitus.

After removing 1 trial in which the intervention period was much longer than those of the other trials (40), the heterogeneities significantly declined to 69%, 0%, 5%, and 38% for TG, TC, LDL cholesterol, and HDL cholesterol in the T2DM subgroup, respectively. However, in the non-T2DM subgroup, the I^2 value for TC decreased from 58% to 0% by omitting 1 arm (33). The reason was that the subjects with NAFLD had been proven to be the main source of heterogeneity for TC by meta-regression analysis. Taken together, the heterogeneities of TG, TC, and HDL cholesterol mainly came from the intervention period, dose of curcuminoids between trials, and the underlying disease.

Compared with 2 existing meta-analyses, there were some similar and controversial conclusions in our meta-analysis. Compared with 1 meta-analysis (42), we included 9 more trials that involved people with metabolic diseases. Another reason might be related to the different disease categories (e.g., healthy, Alzheimer's disease, acute coronary syndrome, T2DM, and obese dyslipidemia). Those factors would deteriorate the credibility of conclusions for the previous meta-analysis. Compared with another meta-analysis (43), we not only included all of the same studies but also analyzed 7 additional trials. Consequently, turmeric and curcumin showed similar results for decreasing TG and LDL cholesterol concentrations, as well as lowering TC in people with MetS. However, we confirmed that turmeric and curcumin also affected TC and HDL cholesterol in overall pooled effects. The evidence from our study might be more powerful because of the larger number of trials and more rigid inclusion criteria. The lipid-lowering effects of turmeric and curcuminoids are likely related to the revealed mechanisms. One study demonstrated that curcumin could regulate lipid metabolism pathways that were affected by statins (53). Another study also showed that curcumin could affect several cellular transduction pathways involved in obesity and metabolic diseases (27). In addition, several studies revealed that curcuminoids could reduce triglyceride and cholesterol by inhibiting the expression of lipogenic factors (54–57). Additionally, curcumin notably decreased IL-6 concentrations, which is known to be an anti-obesity factor (57).

The shortcomings of our study were self-evident. First, heterogeneity of LDL cholesterol was relatively high, and the sources of heterogeneity were not found by subgroup analysis or meta-regression. Second, the data from some trials were calculated with formulas according to the *Cochrane Review Handbook*. This process might be another source of the heterogeneity. Finally, previous studies have shown that formulated curcumin (e.g., piperine, nanoparticles, liposomal) possesses higher bioactivity in comparison with curcumin (58–60). However, this meta-analysis could not prove the theory because of the notable heterogeneity and small quantity of trials. Consequently, more homogeneous and high-quality RCTs should be executed to prove the effects of turmeric and curcuminoids on blood lipids.

In conclusion, the present meta-analysis shows that both turmeric and curcuminoids can significantly decrease TG, TC, and LDL cholesterol, and elevate HDL cholesterol concentration in adults with metabolic diseases, and that the curative efficacy is enhanced by prolonging treatment time to >8 wk and increasing the dose to >300 mg/d of curcuminoids.

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